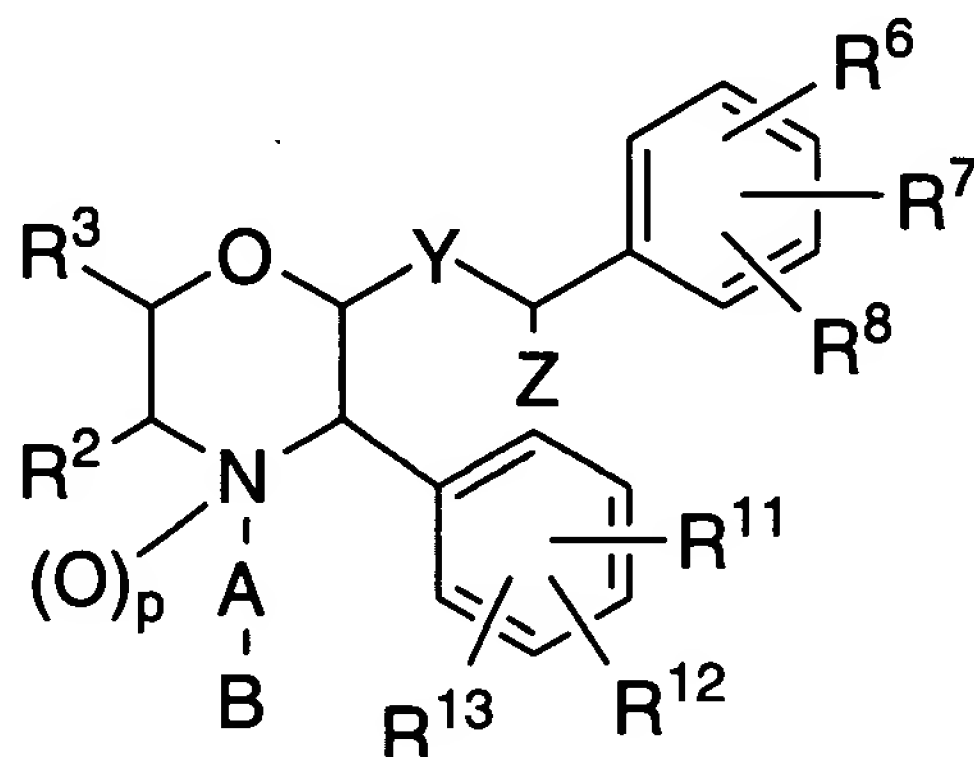


31. A compound of structural formula:



or a pharmaceutically acceptable salt thereof, wherein:

R² and R³ are independently selected from the group consisting of:

- (1) hydrogen,
- (2) C₁-6 alkyl, unsubstituted or substituted with one or more of the substituents selected from:
 - (a) hydroxy,
 - (b) oxo,
 - (c) C₁-6 alkoxy,
 - (d) phenyl-C₁-3 alkoxy,
 - (e) phenyl,
 - (f) -CN,
 - (g) halo,
 - (h) -NR⁹R¹⁰, wherein R⁹ and R¹⁰ are independently selected from:
 - (i) hydrogen,
 - (ii) C₁-6 alkyl,
 - (iii) hydroxy-C₁-6 alkyl, and
 - (iv) phenyl,
 - (i) -NR⁹COR¹⁰,
 - (j) -NR⁹CO₂R¹⁰,
 - (k) -CONR⁹R¹⁰,

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- (l) -COR⁹, and
 - (m) -CO₂R⁹;
- (3) C₂-6 alkenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:
- (a) hydroxy,
 - (b) oxo,
 - (c) C₁-6 alkoxy,
 - (d) phenyl-C₁-3 alkoxy,
 - (e) phenyl,
 - (f) -CN,
 - (g) halo,
 - (h) -CONR⁹R¹⁰,
 - (i) -COR⁹,
 - (j) -CO₂R⁹;
- (4) C₂-6 alkynyl;
- (5) phenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:
- (a) hydroxy,
 - (b) C₁-6 alkoxy,
 - (c) C₁-6 alkyl,
 - (d) C₂-5 alkenyl,
 - (e) halo,
 - (f) -CN,
 - (g) -NO₂,
 - (h) -CF₃,
 - (i) -(CH₂)_m-NR⁹R¹⁰, wherein m is 0, 1 or 2,
 - (j) -NR⁹COR¹⁰,
 - (k) -NR⁹CO₂R¹⁰,
 - (l) -CONR⁹R¹⁰,
 - (m) -CO₂NR⁹R¹⁰,
 - (n) -COR⁹, and

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(o) $-\text{CO}_2\text{R}^9$;

or the groups R^2 and R^3 are joined together to form a carbocyclic ring selected from the group consisting of:

- (a) cyclopentyl,
- (b) cyclohexyl,
- (c) phenyl,

and wherein the carbocyclic ring is unsubstituted or substituted with one or more substituents selected from:

- (i) C_{1-6} alkyl,
- (ii) C_{1-6} alkoxy,
- (iii) $-\text{NR}^9\text{R}^{10}$,
- (iv) halo, and
- v) trifluoromethyl;

or the groups R^2 and R^3 are joined together to form a heterocyclic ring selected from the group consisting of:

- (a) pyrrolidinyl,
- (b) piperidinyl,
- (c) pyrrolyl,
- (d) pyridinyl,
- (e) imidazolyl,
- (f) furanyl,
- (g) oxazolyl,
- (h) thienyl, and
- (i) thiazolyl,

and wherein the heterocyclic ring is unsubstituted or substituted with one or more substituent(s) selected from:

- (i) C_{1-6} alkyl,
- (ii) oxo,
- (iii) C_{1-6} alkoxy,
- (iv) $-\text{NR}^9\text{R}^{10}$,

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- (v) halo, and
- (vi) trifluoromethyl;

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R6, R7 and R8 are independently selected from the group consisting of:

- (1) hydrogen;
- (2) C1-6 alkyl, unsubstituted or substituted with one or more of the substituents selected from:
 - (a) hydroxy,
 - (b) oxo,
 - (c) C1-6 alkoxy,
 - (d) phenyl-C1-3 alkoxy,
 - (e) phenyl,
 - (f) -CN,
 - (g) halo,
 - (h) -NR⁹R¹⁰,
 - (i) -NR⁹COR¹⁰,
 - (j) -NR⁹CO₂R¹⁰,
 - (k) -CONR⁹R¹⁰,
 - (l) -COR⁹, and
 - (m) -CO₂R⁹;
- (3) C2-6 alkenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:
 - (a) hydroxy,
 - (b) oxo,
 - (c) C1-6 alkoxy,
 - (d) phenyl-C1-3 alkoxy,
 - (e) phenyl,
 - (f) -CN,
 - (g) halo,
 - (h) -CONR⁹R¹⁰,
 - (i) -COR⁹, and
 - (j) -CO₂R⁹;

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- (4) C2-6 alkynyl;
 - (5) phenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:
 - (a) hydroxy,
 - (b) C1-6 alkoxy,
 - (c) C1-6 alkyl,
 - (d) C2-5 alkenyl,
 - (e) halo,
 - (f) -CN,
 - (g) -NO₂,
 - (h) -CF₃,
 - (i) -(CH₂)_m-NR⁹R¹⁰,
 - (j) -NR⁹COR¹⁰,
 - (k) -NR⁹CO₂R¹⁰,
 - (l) -CONR⁹R¹⁰,
 - (m) -CO₂NR⁹R¹⁰,
 - (n) -COR⁹, and
 - (o) -CO₂R⁹;
 - (6) halo,
 - (7) -CN,
 - (8) -CF₃,
 - (9) -NO₂,
 - (10) -SR¹⁴, wherein R¹⁴ is hydrogen or C1-5alkyl,
 - (11) -SOR¹⁴,
 - (12) -SO₂R¹⁴,
 - (13) NR⁹COR¹⁰,
 - (14) CONR⁹COR¹⁰,
 - (15) NR⁹R¹⁰,
 - (16) NR⁹CO₂R¹⁰,
 - (17) hydroxy,
 - (18) C1-6alkoxy,
 - (19) COR⁹,

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- (20) CO₂R⁹,
 - (21) 2-pyridyl,
 - (22) 3-pyridyl,
 - (23) 4-pyridyl,
 - (24) 5-tetrazolyl,
 - (25) 2-oxazolyl, and
 - (26) 2-thiazolyl;

R¹¹, R¹² and R¹³ are independently selected from the definitions of R⁶, R⁷ and R⁸, or -OX;

A is selected from the group consisting of:

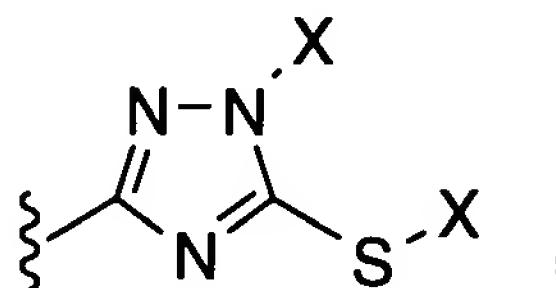
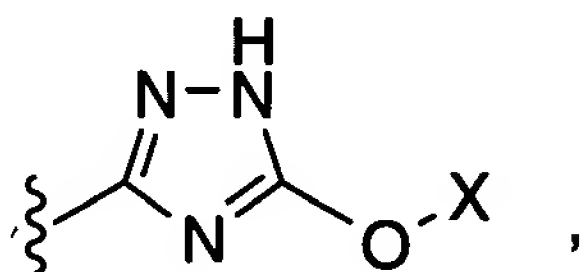
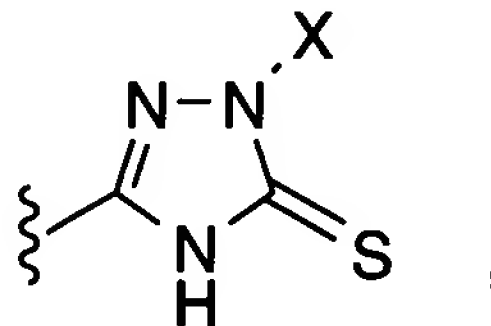
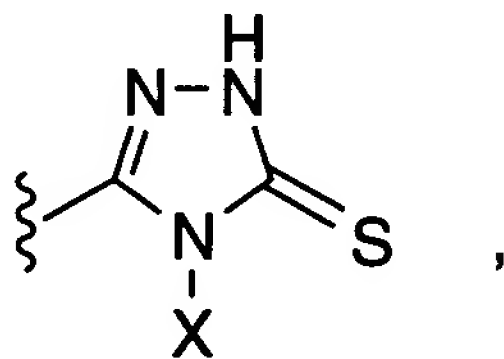
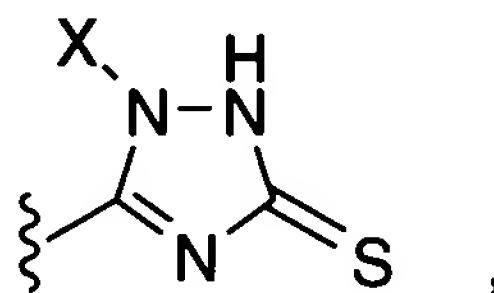
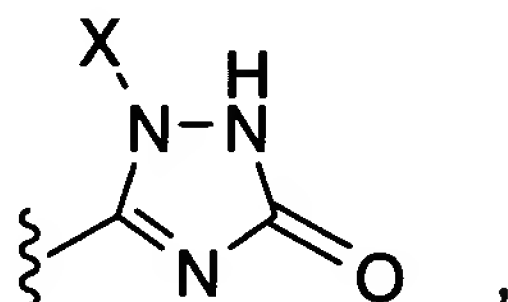
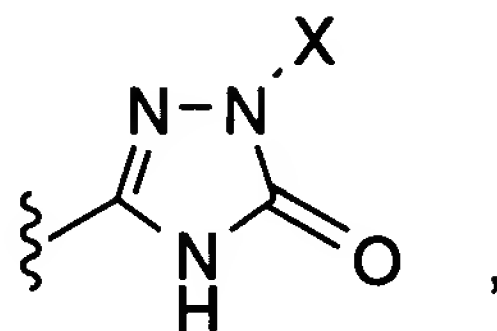
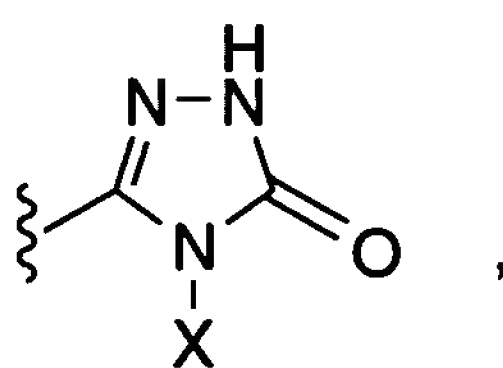
- (1) C₁₋₆ alkyl, unsubstituted or substituted with one or more of the substituents selected from:
 - (a) hydroxy,
 - (b) oxo,
 - (c) C₁₋₆ alkoxy,
 - (d) phenyl-C₁₋₃ alkoxy,
 - (e) phenyl,
 - (f) -CN,
 - (g) halo, wherein halo is fluoro, chloro, bromo or iodo,
 - (h) -NR⁹R¹⁰,
 - (i) -NR⁹COR¹⁰,
 - (j) -NR⁹CO₂R¹⁰,
 - (k) -CONR⁹R¹⁰,
 - (l) -COR⁹, and
 - (m) -CO₂R⁹;
- (2) C₂₋₆ alkenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:
 - (a) hydroxy,
 - (b) oxo,

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- (c) C₁-6 alkoxy,
 (d) phenyl-C₁-3 alkoxy,
 (e) phenyl,
 (f) -CN,
 (g) halo,
 (h) -CONR⁹R¹⁰,
 (i) -COR⁹, and
 (j) -CO₂R⁹; and

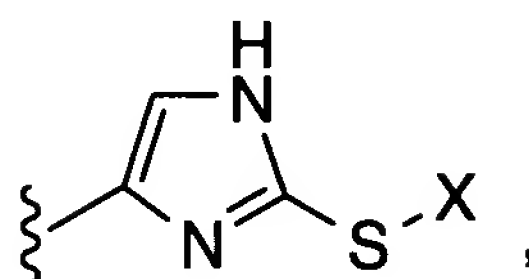
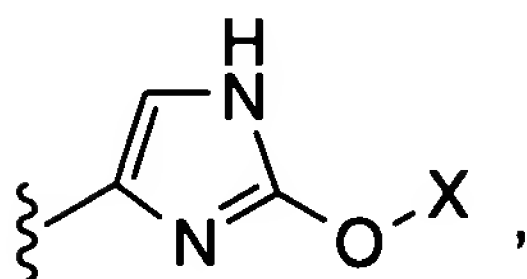
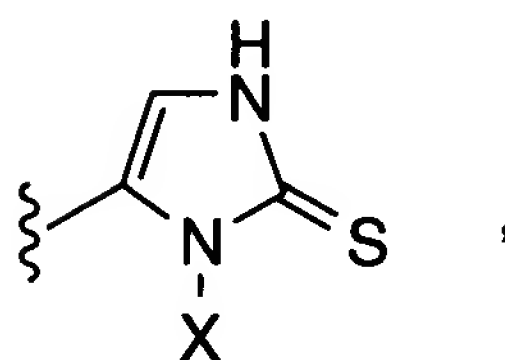
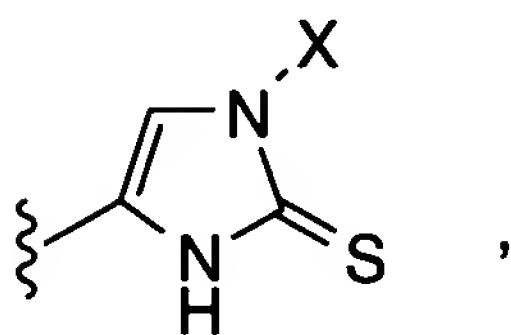
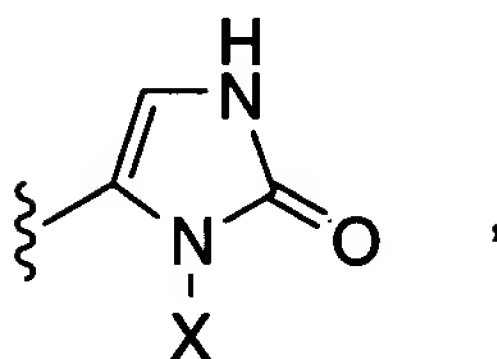
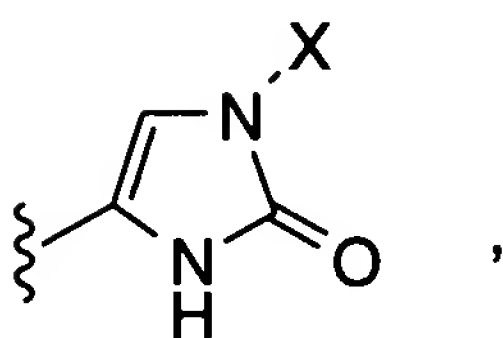
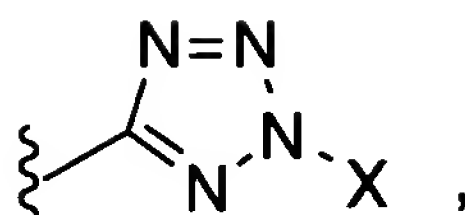
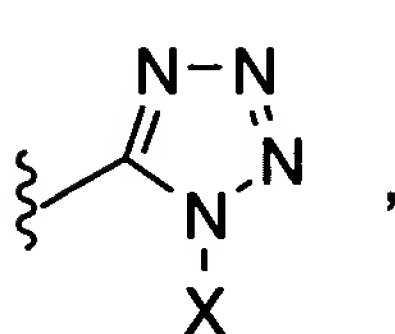
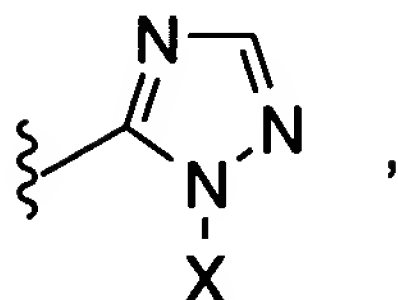
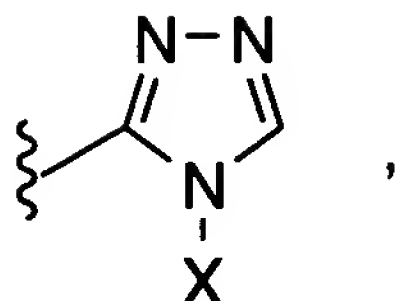
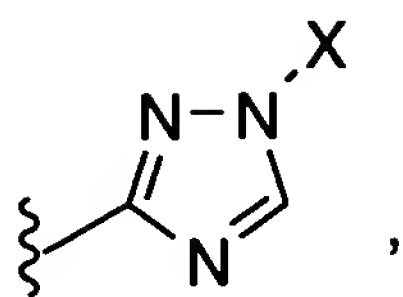
(3) C₂-6 alkynyl;

B is a heterocycle, wherein the heterocycle is selected from the group consisting of:

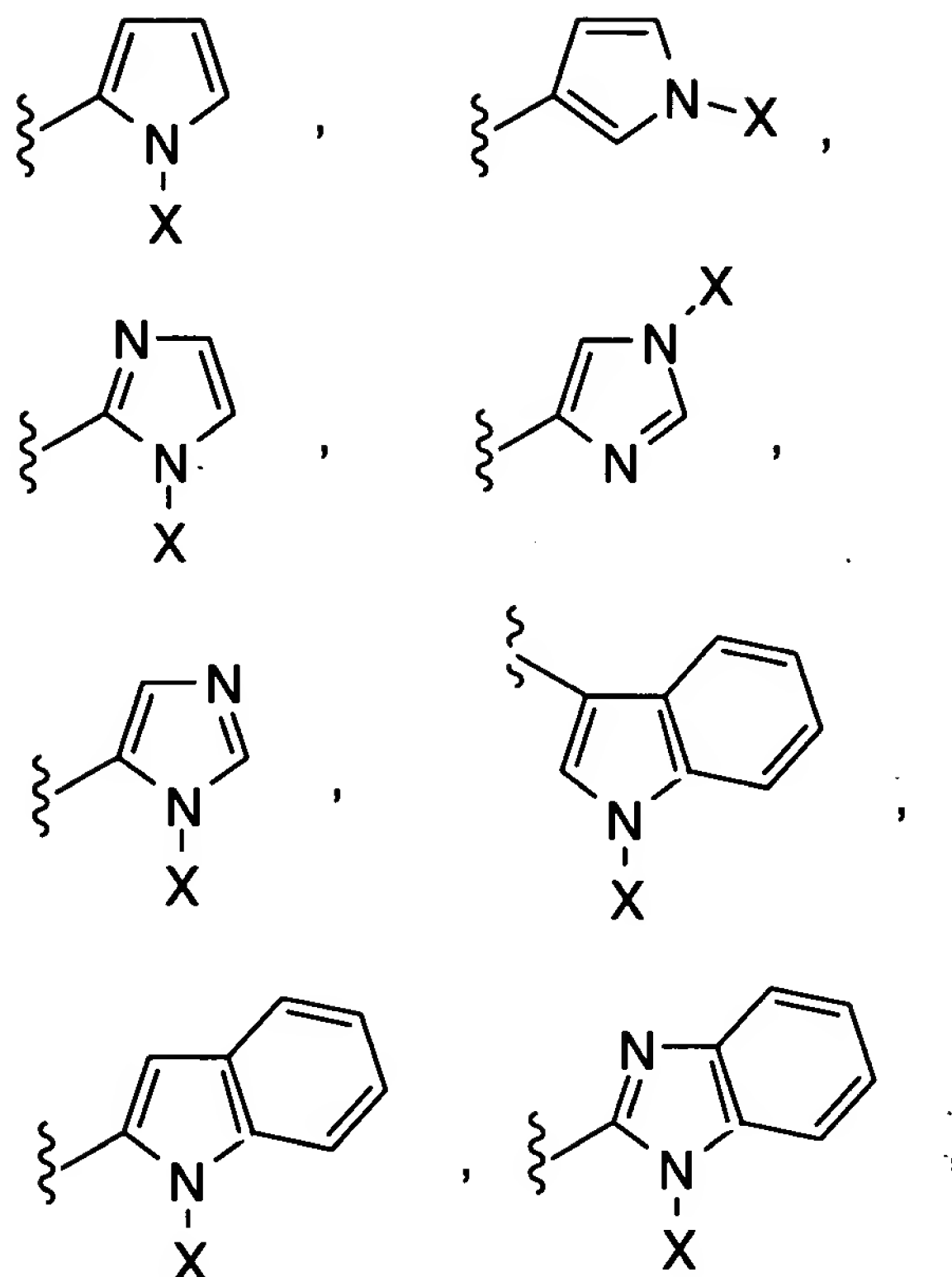


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and wherein the heterocycle is substituted in addition to -X with one or more substituent(s) selected from:

- (i) hydrogen;
- (ii) C1-6 alkyl, unsubstituted or substituted with halo, -CF₃, -OCH₃, or phenyl,
- (iii) C1-6 alkoxy,
- (iv) oxo,
- (v) hydroxy,
- (vi) thioxo,
- (vii) -SR⁹,
- (viii) halo,
- (ix) cyano,
- (x) phenyl,
- (xi) trifluoromethyl,
- (xii) -(CH₂)_m-NR⁹R¹⁰,
- (xiii) -NR⁹COR¹⁰,

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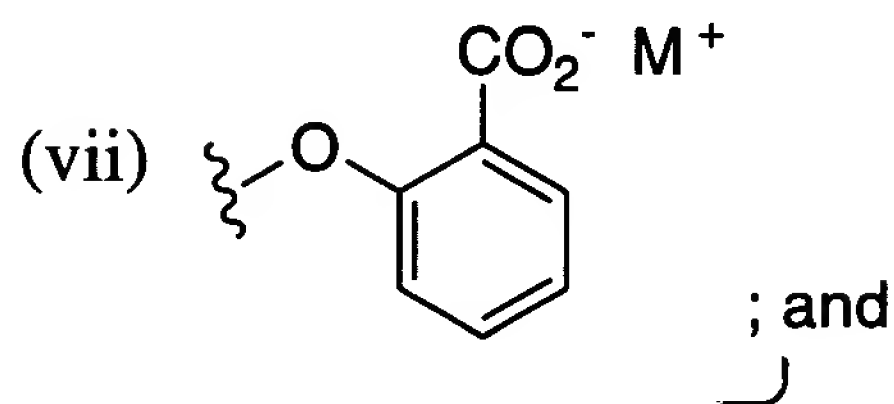
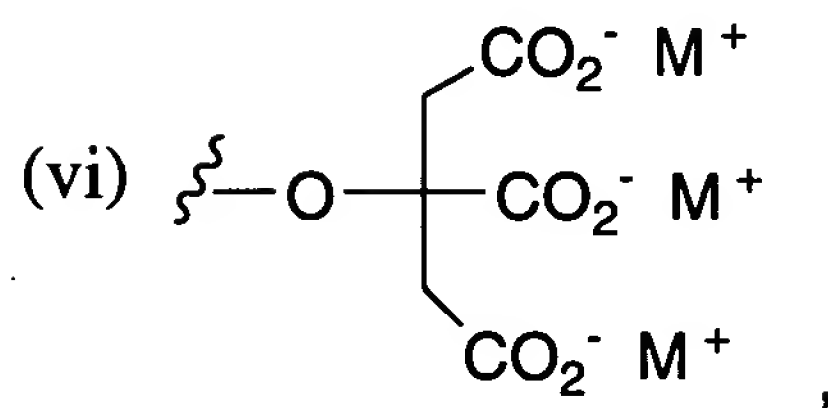
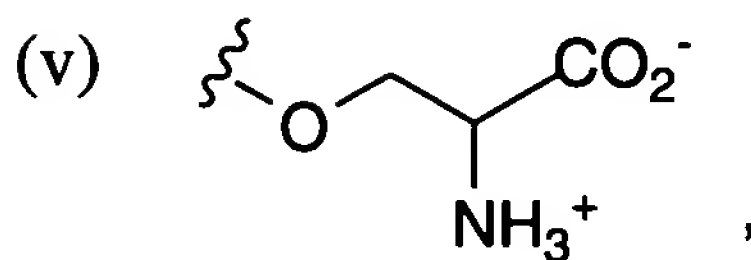
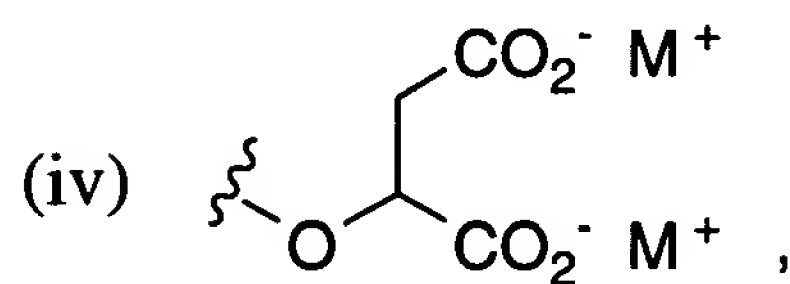
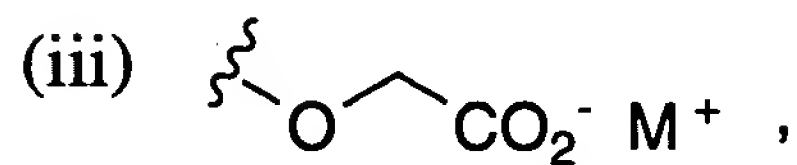
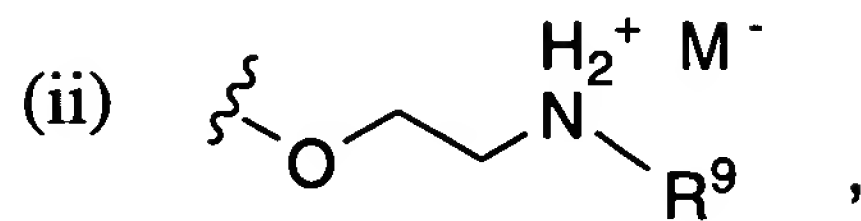
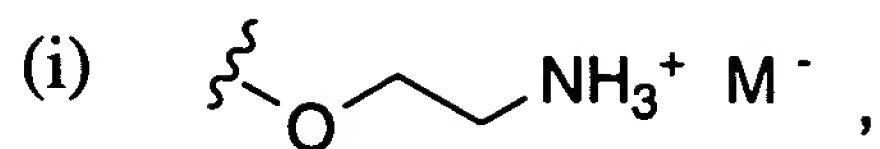
- (xiv) $-\text{CONR}^9\text{R}^{10}$,
(xv) $-\text{CO}_2\text{R}^9$, and
(xvi) $-(\text{CH}_2)_m-\text{OR}^9$;

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p is 0 or 1;

X is selected from:

- (a) $-\text{PO}(\text{OH})\text{O}^- \cdot \text{M}^+$, wherein M^+ is a pharmaceutically acceptable monovalent counterion,
(b) $-\text{PO}(\text{O}^-)_2 \cdot 2\text{M}^+$,
(c) $-\text{PO}(\text{O}^-)_2 \cdot \text{D}^{2+}$, wherein D^{2+} is a pharmaceutically acceptable divalent counterion,
(d) $-\text{CH}(\text{R}^4)-\text{PO}(\text{OH})\text{O}^- \cdot \text{M}^+$, wherein R^4 is hydrogen or C1-3 alkyl,
(e) $-\text{CH}(\text{R}^4)-\text{PO}(\text{O}^-)_2 \cdot 2\text{M}^+$,
(f) $-\text{CH}(\text{R}^4)-\text{PO}(\text{O}^-)_2 \cdot \text{D}^{2+}$,
(g) $-\text{SO}_3^- \cdot \text{M}^+$,
(h) $-\text{CH}(\text{R}^4)-\text{SO}_3^- \cdot \text{M}^+$,
(i) $-\text{CO}-\text{CH}_2\text{CH}_2-\text{CO}_2^- \cdot \text{M}^+$,
(j) $-\text{CH}(\text{CH}_3)-\text{O}-\text{CO}-\text{R}^5$, wherein R^5 is selected from the group consisting of:

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- (k) hydrogen, with the proviso that if p is 0 and none of R¹¹, R¹² or R¹³ are -OX, then X is other than hydrogen;

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Y is selected from the group consisting of:

- Alkyl*
- (1) a single bond,
 - (2) -O-,
 - (3) -S-,
 - (4) -CO-,
 - (5) -CH₂-,
 - (6) -CHR¹⁵-, and
 - (7) -CR¹⁵R¹⁶-, wherein R¹⁵ and R¹⁶ are independently selected from the group consisting of:

(a) C₁-6 alkyl, unsubstituted or substituted with one or more of the substituents selected from:

- (i) hydroxy,
- (ii) oxo,
- (iii) C₁-6 alkoxy,
- (iv) phenyl-C₁-3 alkoxy,
- (v) phenyl,
- (vi) -CN,
- (vii) halo,
- (viii) -NR⁹R¹⁰,
- (ix) -NR⁹COR¹⁰,
- (x) -NR⁹CO₂R¹⁰,
- (xi) -CONR⁹R¹⁰,
- (xii) -COR⁹, and
- (xiii) -CO₂R⁹;

(b) phenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:

- (i) hydroxy,
- (ii) C₁-6 alkoxy,
- (iii) C₁-6 alkyl,
- (iv) C₂-5 alkenyl,
- (v) halo,
- (vi) -CN,

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- (vii) $-\text{NO}_2$,
 - (viii) $-\text{CF}_3$,
 - (ix) $-(\text{CH}_2)_m-\text{NR}^9\text{R}^{10}$,
 - (x) $-\text{NR}^9\text{COR}^{10}$,
 - (xi) $-\text{NR}^9\text{CO}_2\text{R}^{10}$,
 - (xii) $-\text{CONR}^9\text{R}^{10}$,
 - (xiii) $-\text{CO}_2\text{NR}^9\text{R}^{10}$,
 - (xiv) $-\text{COR}^9$, and
 - (xv) $-\text{CO}_2\text{R}^9$;

Z is selected from:

- (1) hydrogen,
- (2) C1-6 alkyl, and
- (3) hydroxy, with the proviso that if Y is $-\text{O}-$, then Z is other than hydroxy,
and with the further proviso that if Y is $-\text{CHR}^{15}-$, then Z and R^{15} may be joined together to form a double bond between the two carbon atoms.

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~~32~~. The compound of Claim ~~1~~ wherein:

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R² and R³ are independently selected from the group consisting of:

- (1) hydrogen,
- (2) C₁-6 alkyl,
- (3) C₂-6 alkenyl, and
- (4) phenyl;

R⁶, R⁷ and R⁸ are independently selected from the group consisting of:

- (1) hydrogen,
- (2) C₁-6 alkyl,
- (3) fluoro,
- (4) chloro,
- (5) bromo,
- (6) iodo, and
- (7) -CF₃;

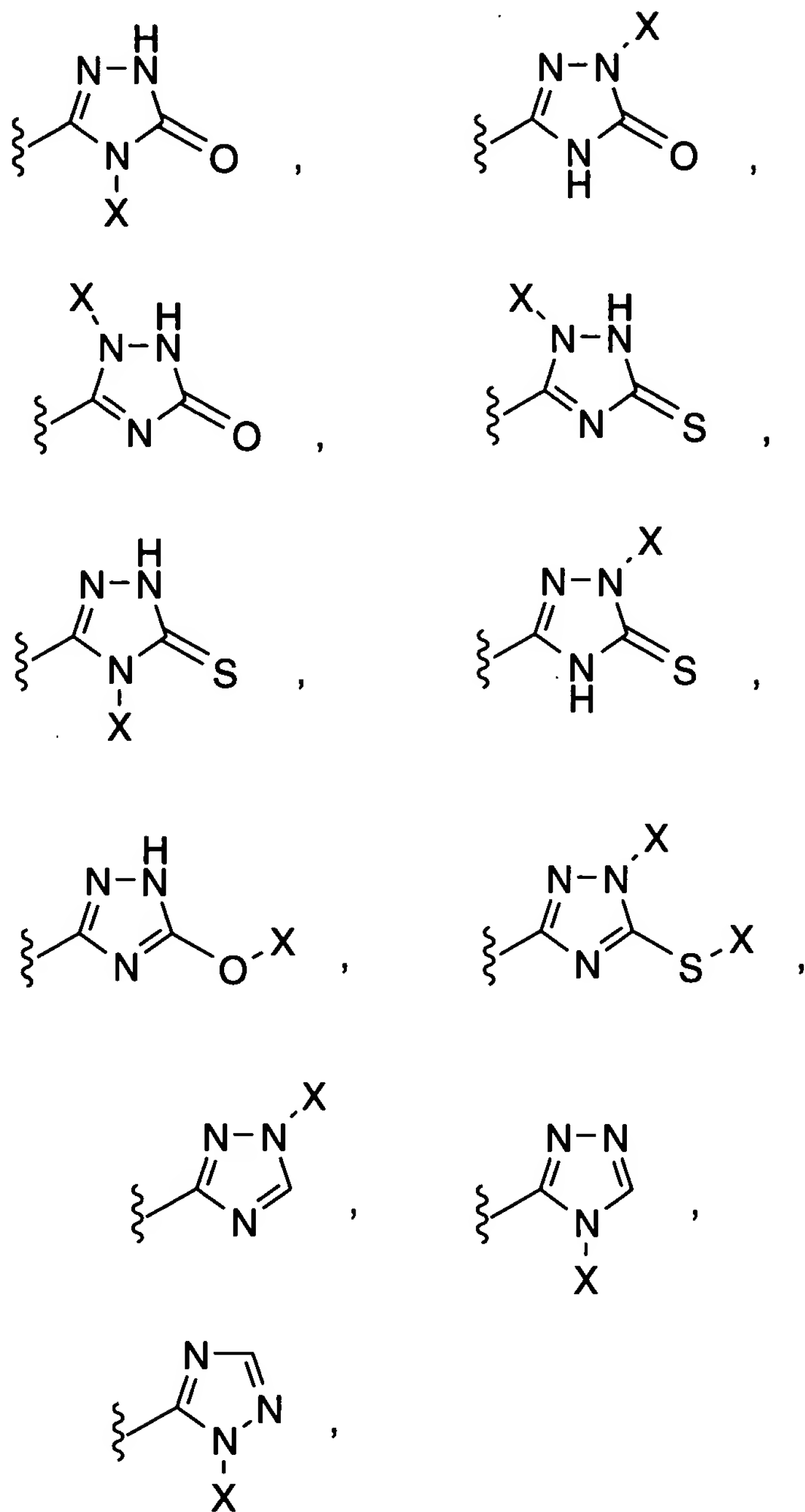
R¹¹, R¹² and R¹³ are independently selected from the group consisting of:

- (1) fluoro,
- (2) chloro,
- (3) bromo, and
- (4) iodo;

A is unsubstituted C₁-6 alkyl;

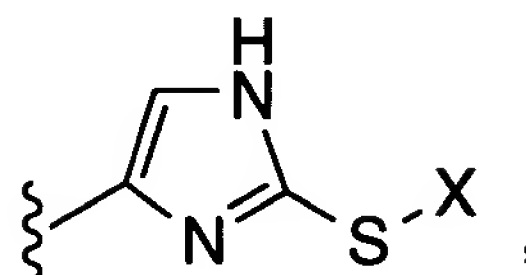
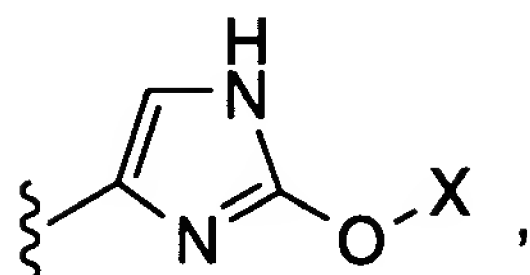
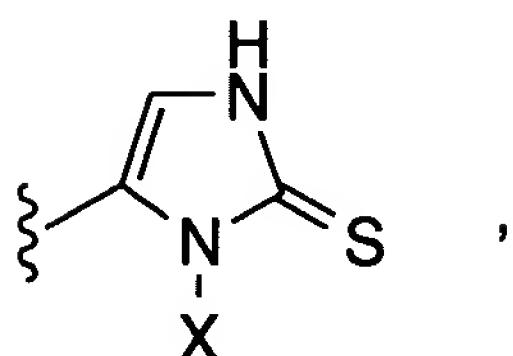
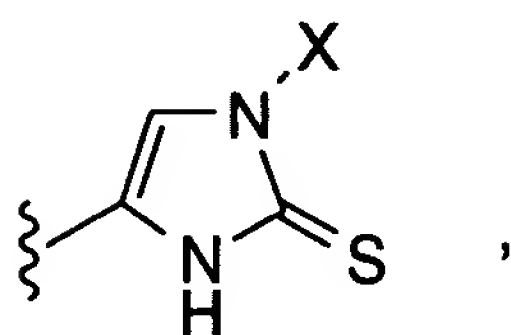
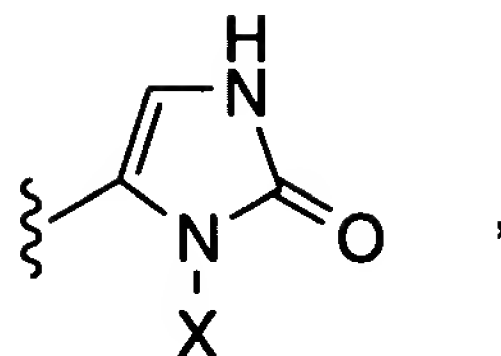
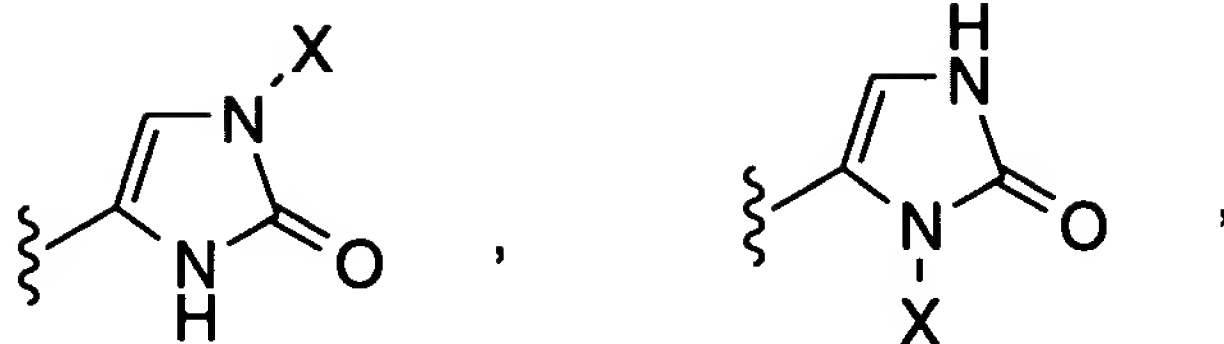
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B is selected from the group consisting of:



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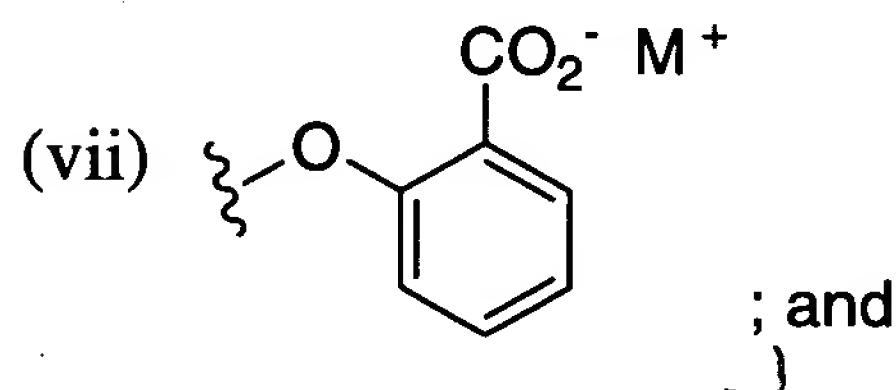
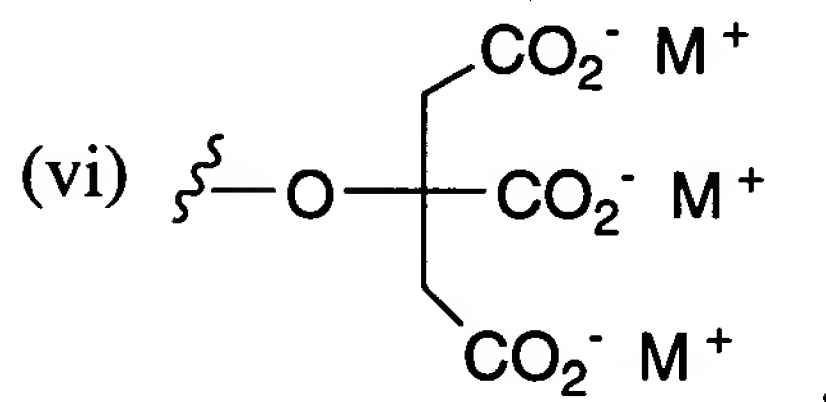
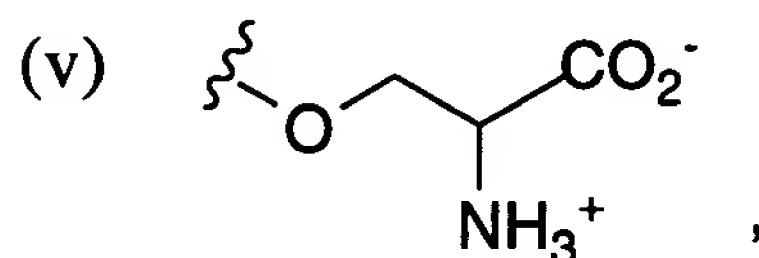
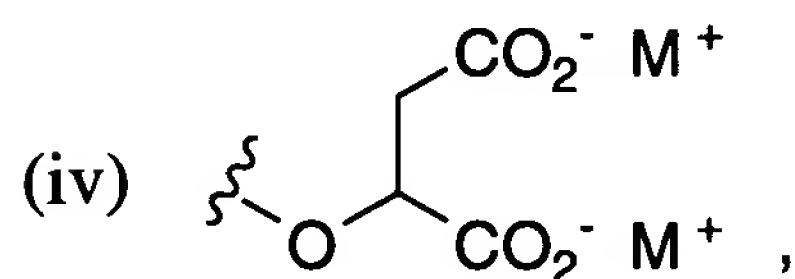
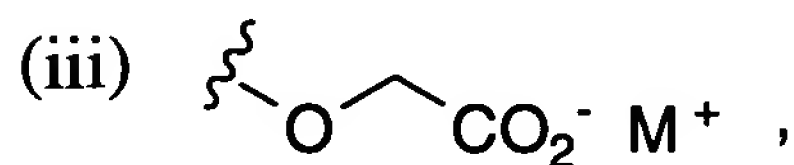
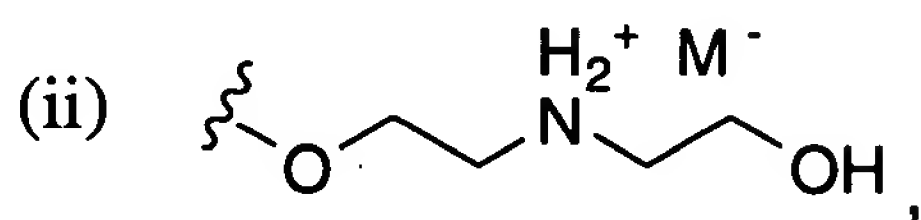
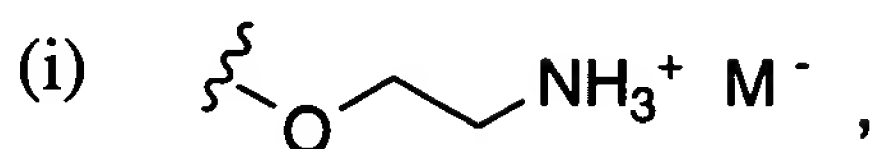


p is 0;

X is selected from:

- (a) $-\text{PO}(\text{OH})\text{O}^- \cdot \text{M}^+$, wherein M^+ is a pharmaceutically acceptable monovalent counterion,
- (b) $-\text{PO}(\text{O}^-)_2 \cdot 2\text{M}^+$,
- (c) $-\text{PO}(\text{O}^-)_2 \cdot \text{D}^{2+}$, wherein D^{2+} is a pharmaceutically acceptable divalent counterion,
- (d) $-\text{CH}(\text{R}^4)-\text{PO}(\text{OH})\text{O}^- \cdot \text{M}^+$, wherein R^4 is hydrogen or methyl,
- (e) $-\text{CH}(\text{R}^4)-\text{PO}(\text{O}^-)_2 \cdot 2\text{M}^+$,
- (f) $-\text{CH}(\text{R}^4)-\text{PO}(\text{O}^-)_2 \cdot \text{D}^{2+}$,
- (g) $-\text{CO}-\text{CH}_2\text{CH}_2-\text{CO}_2^- \cdot \text{M}^+$,

(h) $-\text{CH}(\text{CH}_3)-\text{O}-\text{CO}-\text{R}^5$, wherein R^5 is selected from the group consisting of:



Y is $-\text{O}-$;

Z is hydrogen or C1-4 alkyl.

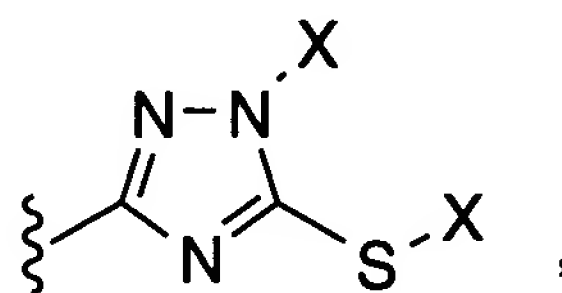
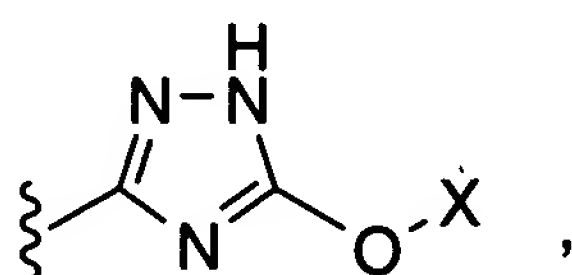
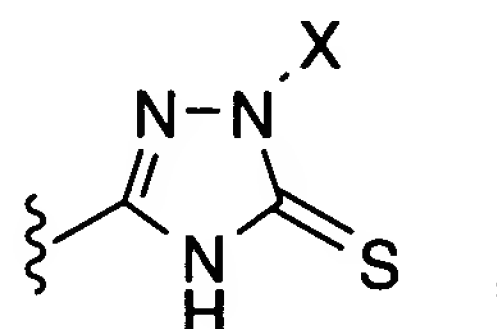
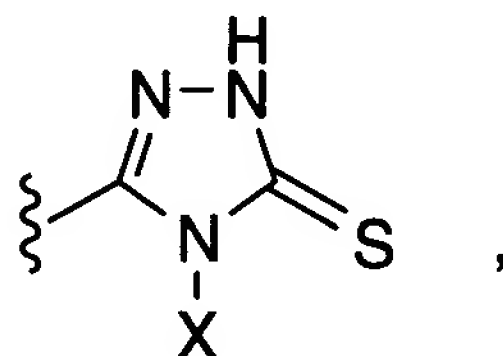
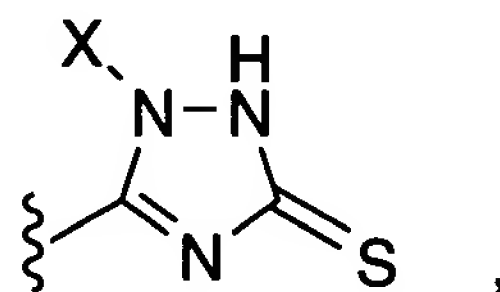
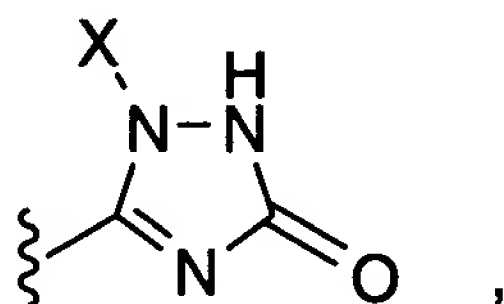
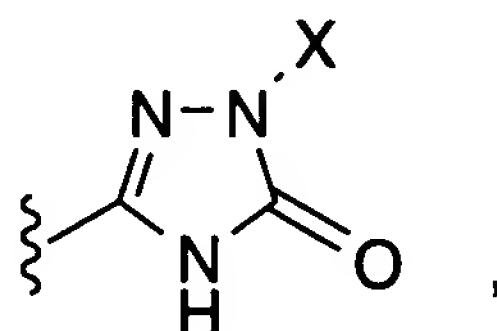
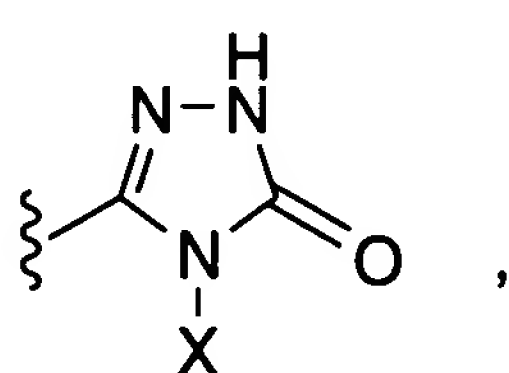
262

³
~~33.~~ The compound of Claim ~~31~~ wherein Z is C₁₋₄ alkyl.

⁴
~~34.~~ The compound of Claim ~~31~~ wherein Z is -CH₃.

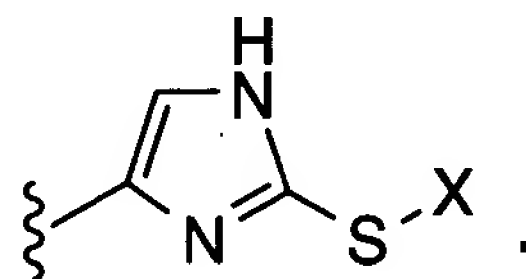
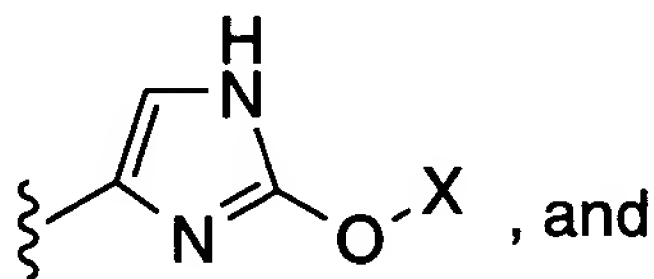
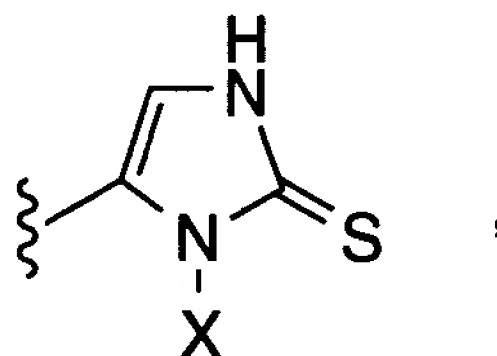
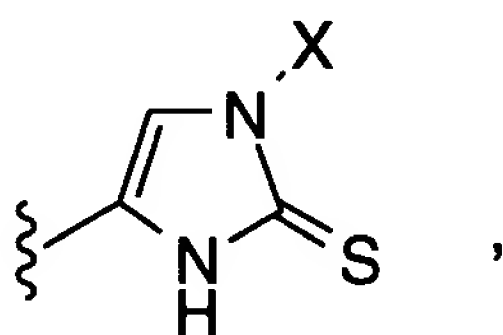
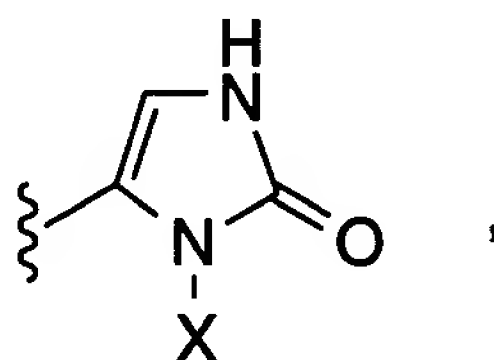
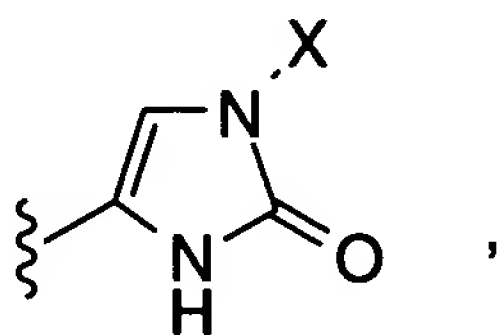
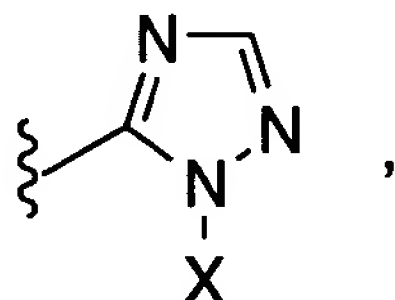
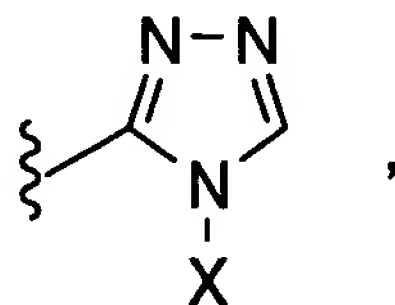
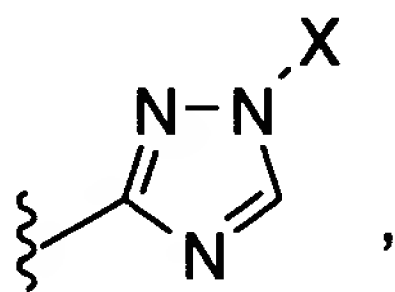
⁵
~~35.~~ The compound of Claim ~~31~~ wherein A is -CH₂- or -CH(CH₃)-.

⁶
~~36.~~ The compound of Claim ~~31~~ wherein -B is selected from the group consisting of:



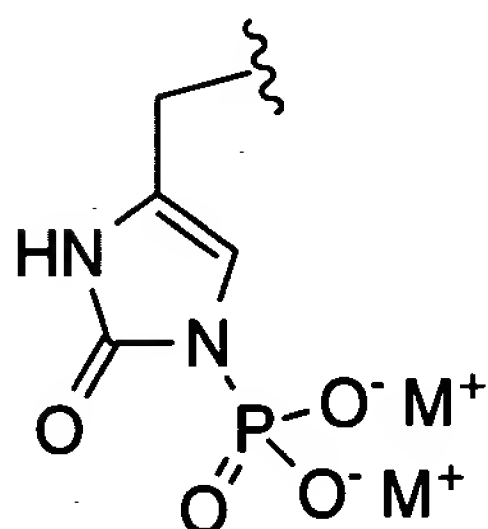
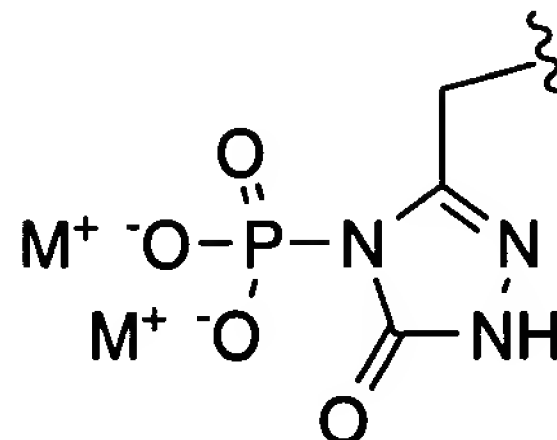
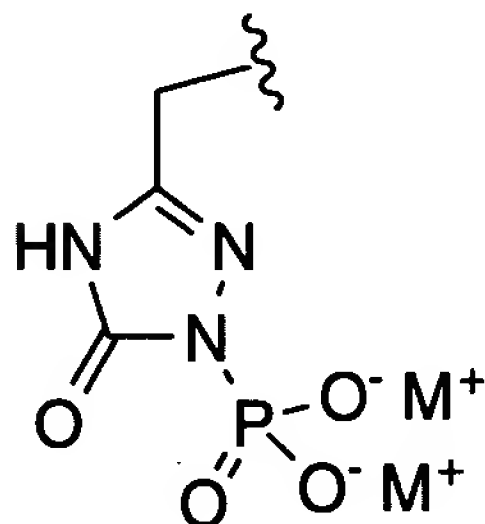
263

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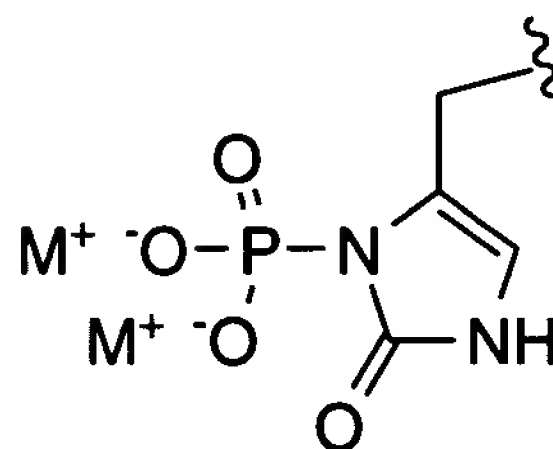


264

²
~~37~~. The compound of Claim ~~31~~¹ wherein -A-B is selected from the group consisting of:



, and



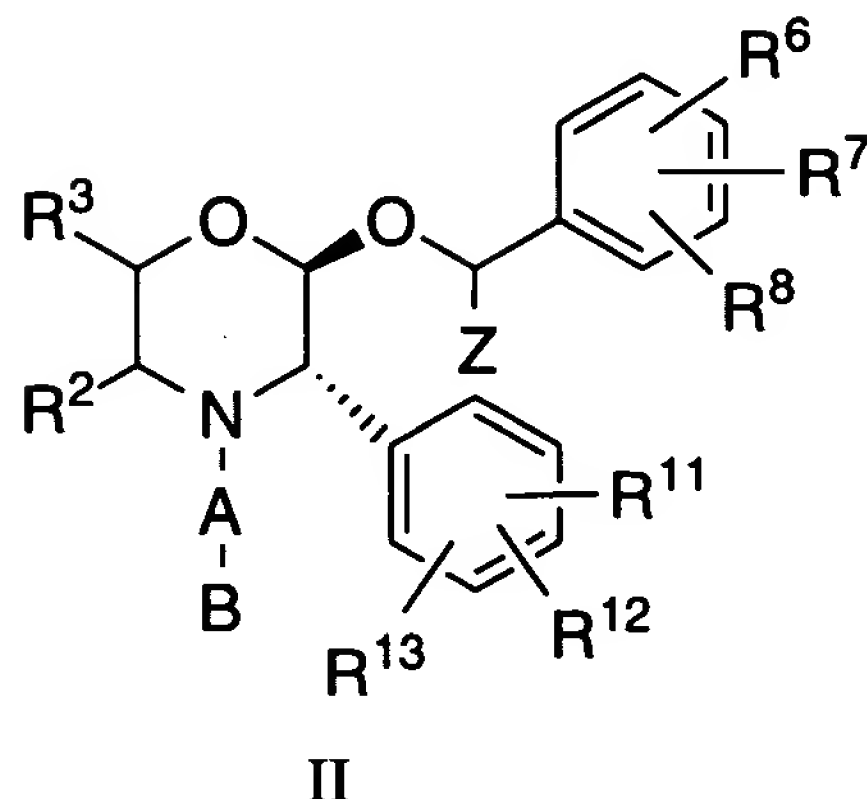
⁸
~~38~~. The compound of Claim ~~31~~¹ wherein X is selected from the group consisting of:

- (a) $-\text{PO}(\text{O}^-)_2 \cdot 2\text{M}^+$, wherein M^+ is a pharmaceutically acceptable monovalent counterion, and
- (b) $-\text{PO}(\text{O}^-)_2 \cdot \text{D}^{2+}$, wherein D^{2+} is a pharmaceutically acceptable divalent counterion.

265

formula II:

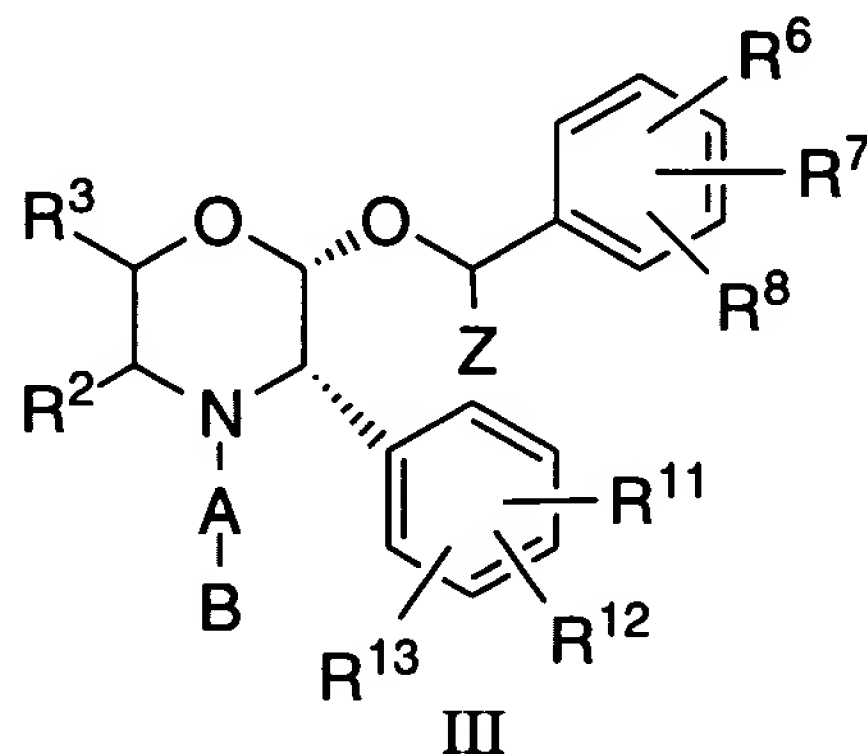
39. The compound of Claim 31 of the structural



or a pharmaceutically acceptable salt thereof, wherein ~~R2, R3, R6, R7, R8, R11, R12, R13, A, B and Z~~ are as defined in Claim 1.

formula III:

40. The compound of Claim 41 of the structural



or a pharmaceutically acceptable salt thereof, wherein ~~R2, R3, R6, R7, R8, R11, R12, R13, A, B, and Z~~ are as defined in Claim 1.

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~~41~~¹¹. A compound which is selected from the group consisting of:

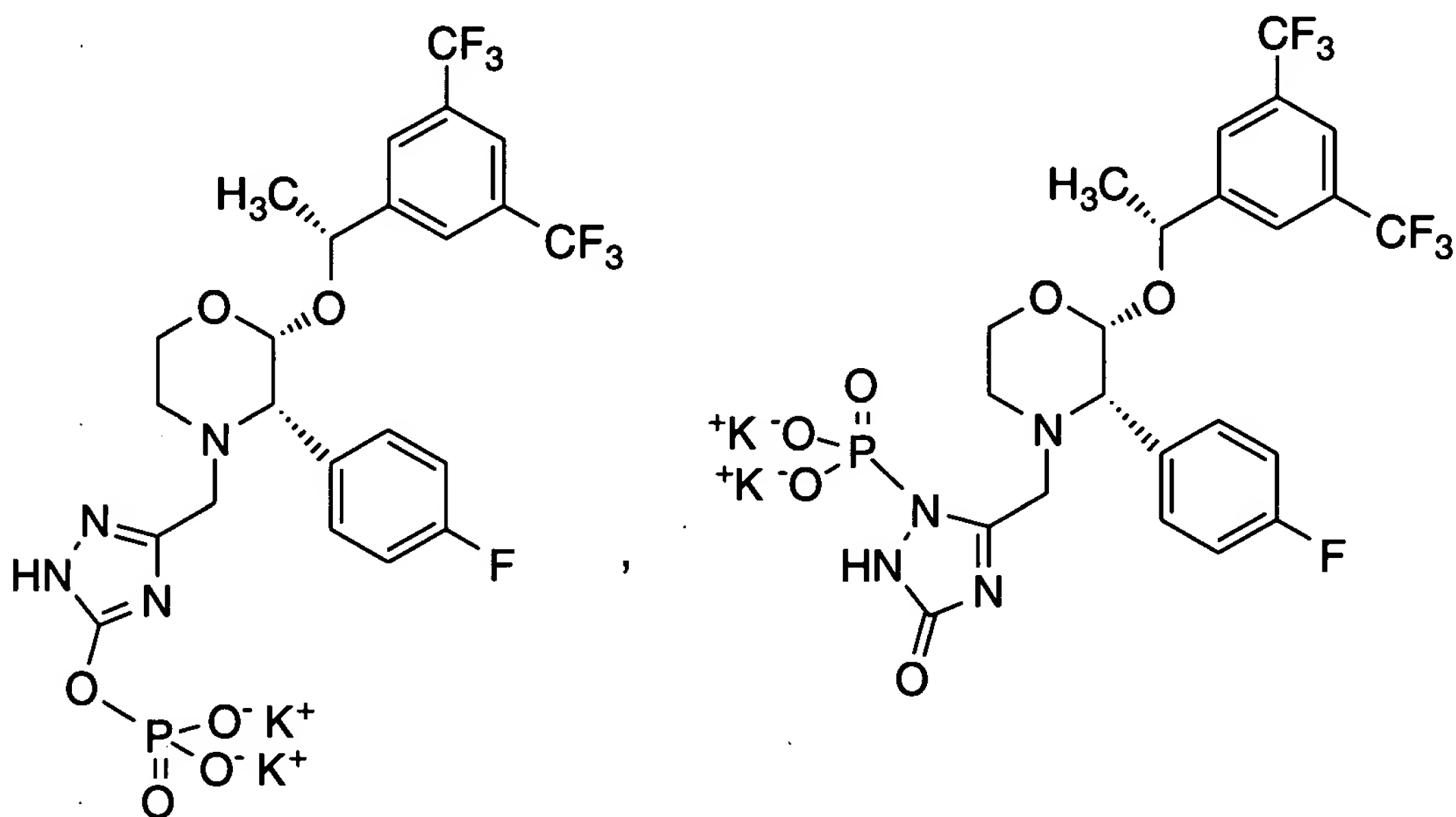
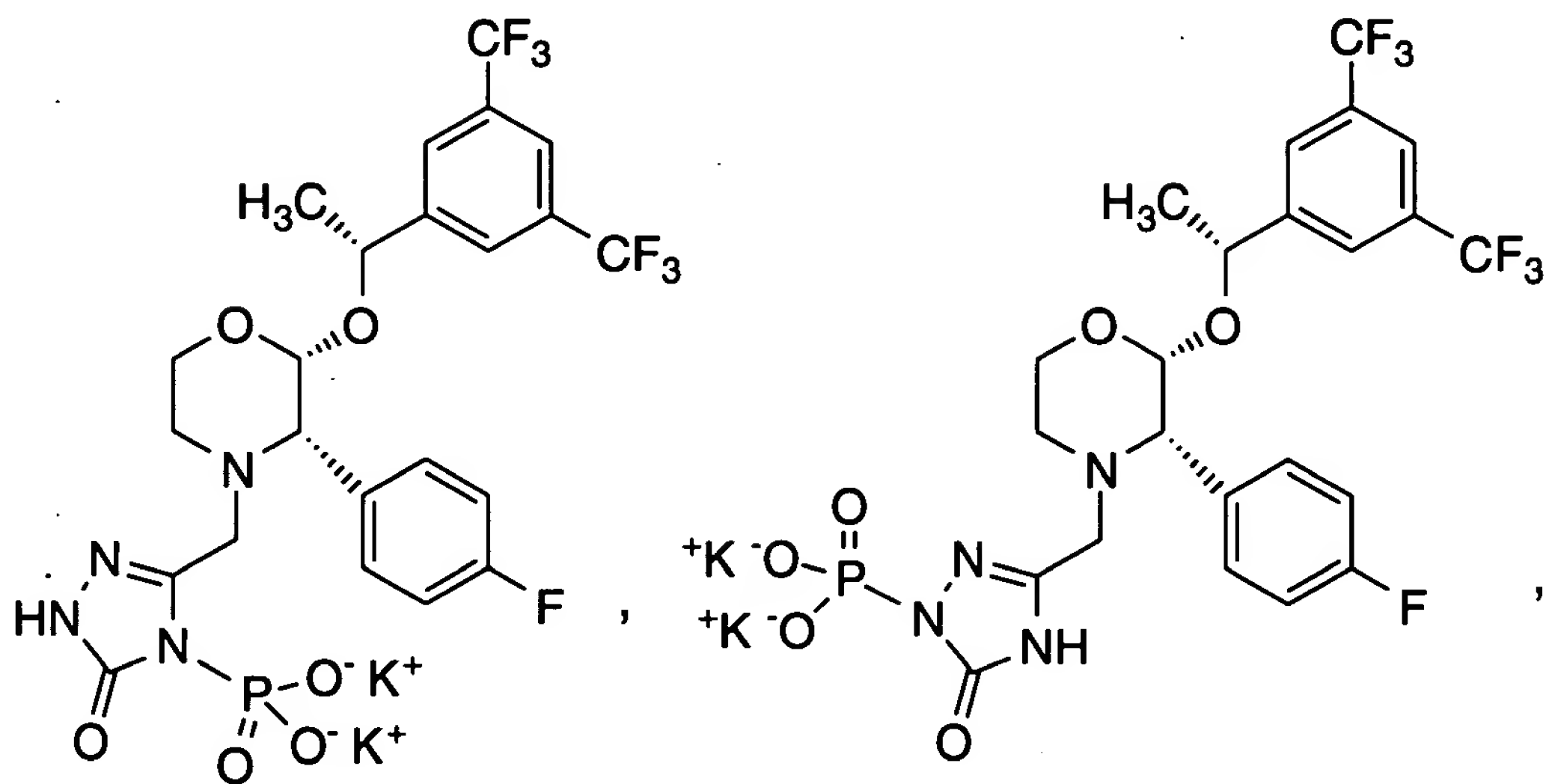
- Al*
Antal
- (1) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine N-oxide;
 - (2) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)-phenyl-4-(3-(4-monophosphoryl-5-oxo-1H-1,2,4-triazolo)methyl)morpholine;
 - (3) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)-phenyl-4-(3-(1-monophosphoryl-5-oxo-1H-1,2,4-triazolo)methyl)morpholine;
 - (4) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)-phenyl-4-(3-(2-monophosphoryl-5-oxo-1H-1,2,4-triazolo)methyl)morpholine;
 - (5) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)-phenyl-4-(3-(5-oxophosphoryl-1H-1,2,4-triazolo)-methyl)morpholine;
 - (6) 2-(S)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)-phenyl-4-(3-(1-phosphoryl-5-oxo-4H-1,2,4-triazolo)methyl)morpholine;

or a pharmaceutically acceptable salt thereof.

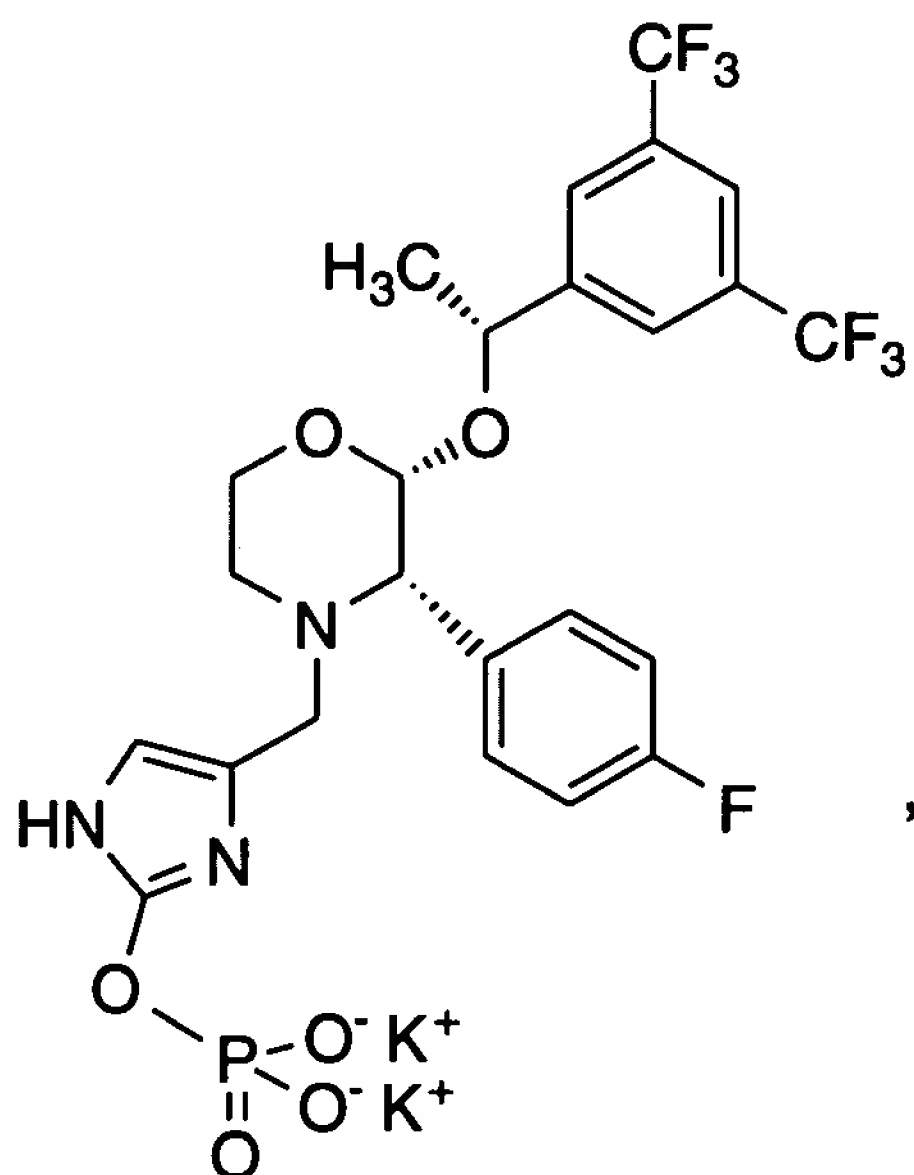
~~42~~¹¹². The compound of Claim ~~41~~¹¹¹ wherein the pharmaceutically acceptable salt is the bis(N-methyl-D-glucamine) salt.

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¹³
~~43.~~ A compound which is selected from the group
consisting of:



268



wherein K^+ is a pharmaceutically acceptable counterion.

269

¹⁴
~~44~~

A compound which is:

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-
3-(S)-(4-fluoro)phenyl-4-(3-(1-phosphoryl-5-oxo-
4H-1,2,4-triazolo)methylmorpholine;

or a pharmaceutically acceptable salt thereof.

¹⁵
~~45~~

The compound of Claim ¹⁴~~44~~ wherein the
pharmaceutically acceptable salt is the bis(N-methyl-D-glucamine) salt.

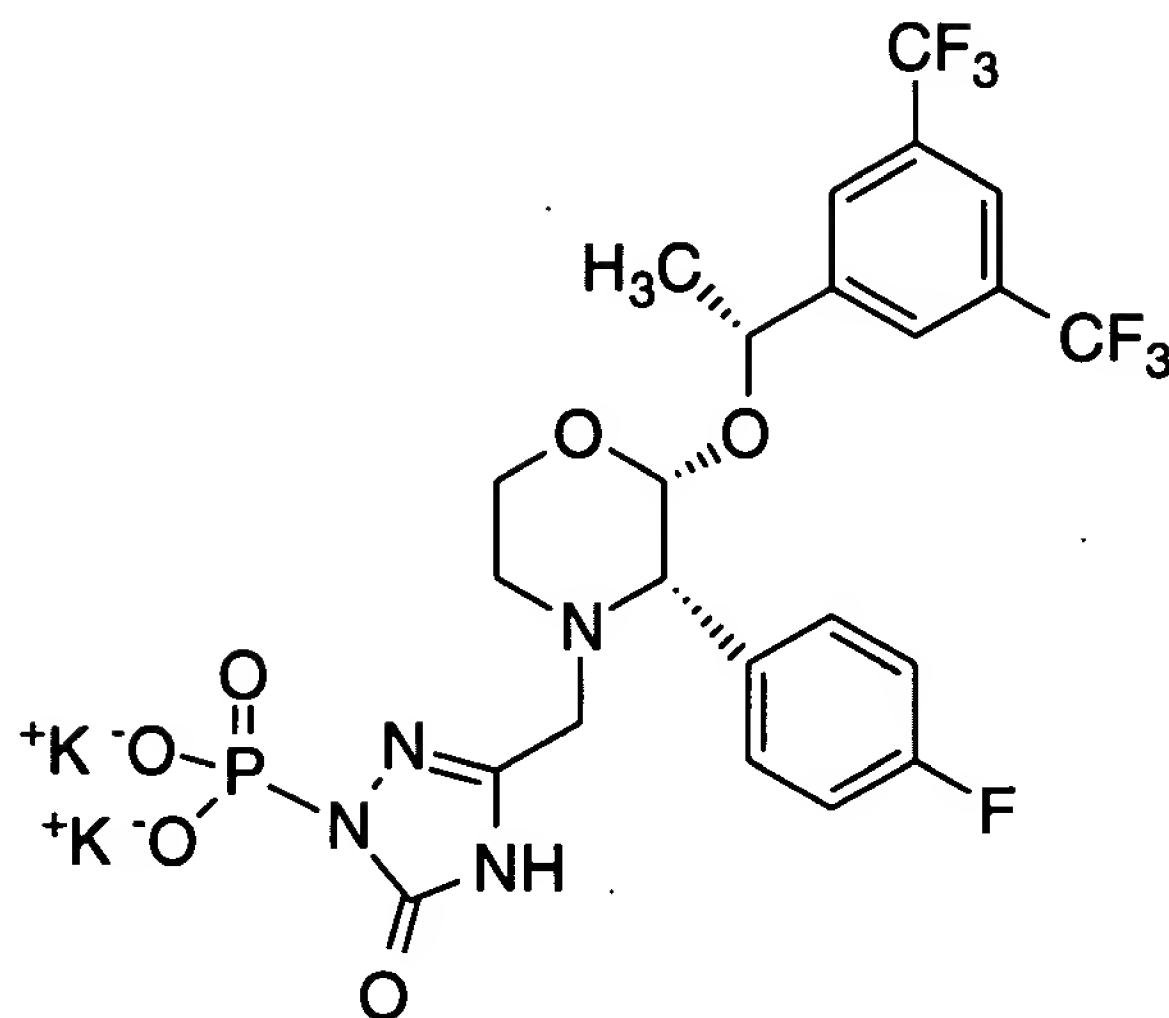
¹⁶
~~46~~

A compound which is

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-
(4-fluoro)phenyl-4-(3-(1-phosphoryl-5-oxo-4H-1,2,4-
triazolo)methylmorpholine, bis(N-methyl-D-glucamine).

270

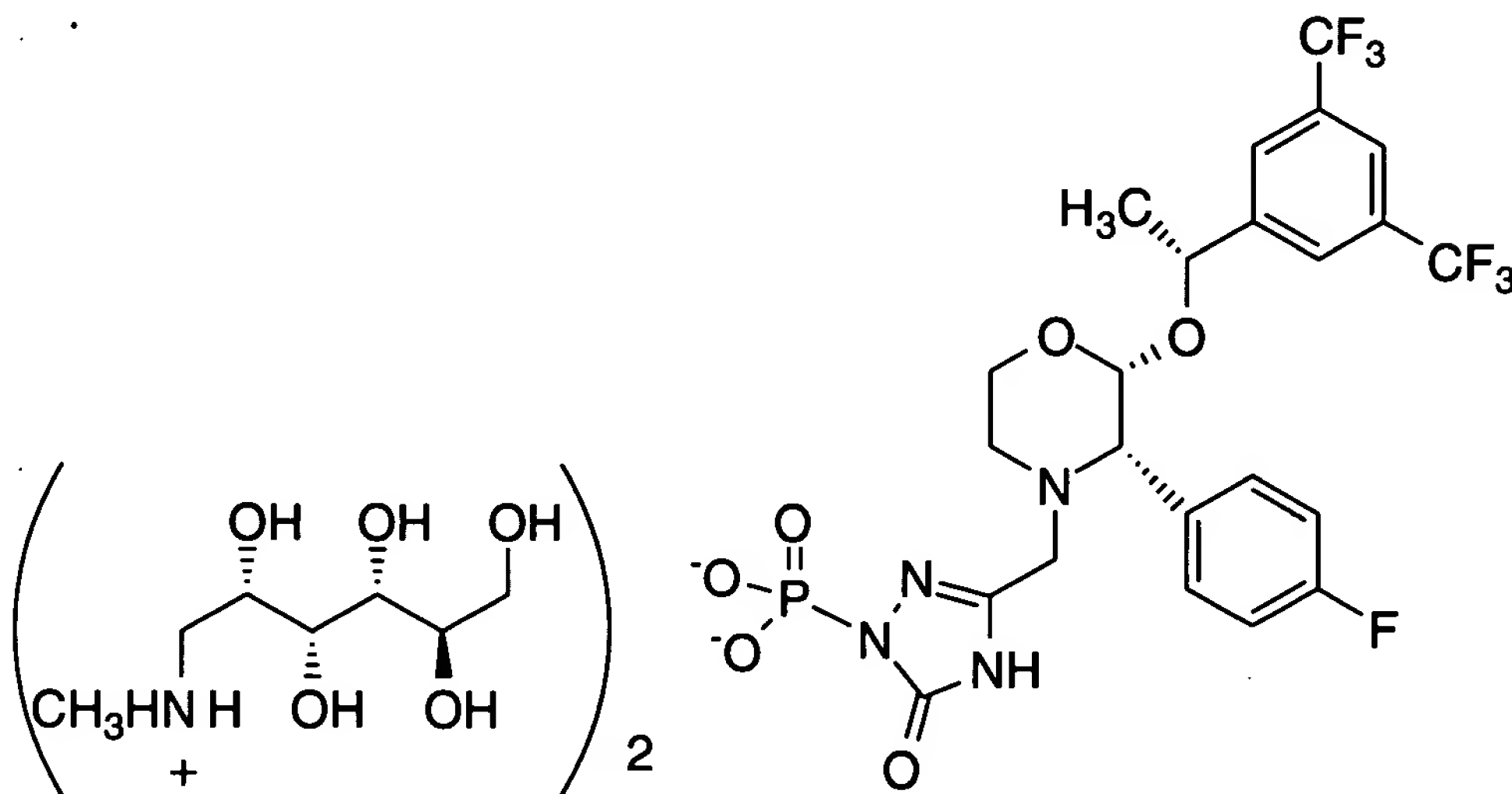
~~17~~
~~47~~. A compound which is:



wherein K^+ is a pharmaceutically acceptable counterion.

~~18~~
~~48~~. The compound of Claim ~~47~~ wherein K^+ is N-methyl-D-glucamine.

~~19~~
~~49~~. A compound which is:



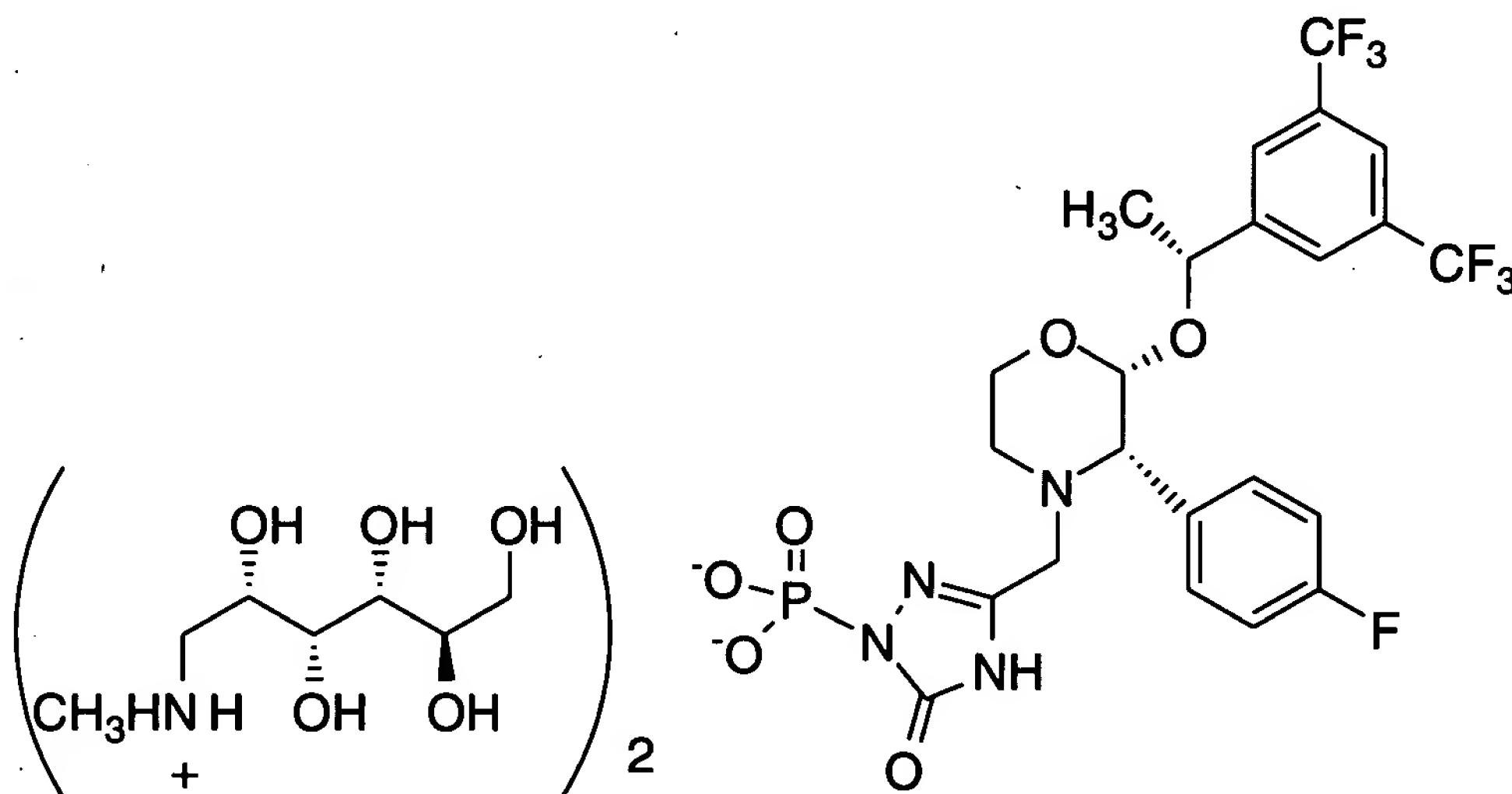
271

²⁰
~~50~~. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of the compound of Claim ~~51~~!

W
Amstel
²¹
~~51~~. The pharmaceutical composition of Claim ~~50~~ wherein the pharmaceutically acceptable carrier comprises water.

²²
~~52~~. The pharmaceutical composition of Claim ~~50~~ wherein the pharmaceutically acceptable carrier comprises a physiologically acceptable saline solution.

²³
~~53~~. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of a compound which is:



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²⁴
~~54.~~ A method for antagonizing the effect of substance P at its receptor site or for the blockade of neurokinin-1 receptors in a mammal which comprises the administration to the mammal of the compound of Claim ~~31~~ in an amount that is effective for antagonizing the effect of substance P at its receptor site or for the blockade of neurokinin-1 receptors in the mammal.

²⁵
~~55.~~ A method of treating or preventing pain or nociception which comprises the administration to the mammal of an effective amount of the compound of Claim ~~31~~!

~~56. A method of treating or preventing a condition~~
selected from the group consisting of: diabetic neuropathy; peripheral neuropathy; AIDS related neuropathy; chemotherapy-induced neuropathy; and neuralgia, in a mammal in need thereof which comprises the administration to the mammal of an effective amount of the compound of Claim 31.

57. A method for the treatment or prevention of asthma in a mammal in need thereof which comprises the administration to the mammal of an effective amount of the compound of Claim 31, either alone or in combination with a neurokinin-2 receptor antagonist or with a β 2-adrenergic receptor agonist.

58. A method for the treatment of cystic fibrosis in a mammal in need thereof which comprises the administration to the mammal of an effective amount of the compound of Claim 31.

59. A method for the treatment or prevention of arthritis in a mammal in need thereof which comprises the administration to the mammal of an effective amount of the compound of Claim 31.